

An amino alcohol ligand and its use in preparation of chiral proparglic tertiary alcohols and tertiary amines *via* enantioselective addition reaction

Technical Field

The invention relates to a process of asymmetric alkynylation of ketone or ketimine, involving the enantioselective addition of terminal alkynes to a trifluoromethyl ketone or ketimine intermediate to give a chiral tertiary proparglic alcohols or amines. The adduct compounds are the key precursors to the potent HIV reverse transcriptase inhibitor Efavirenz (DMP 266), DPC 961 and DPC 083. The invention also relates the new amino alcohol ligand used in the above process.

Background Art

Human immunodeficiency virus (HIV) is prone to mutation, which leads to drug resistance. It is known that some compounds are reverse transcriptase inhibitors and are effective agents in the treatment of HIV, and similar diseases, e.g. azidothymidine or AZT. DPC083 , DPC 961 and Efavirenz (Sustiva TM) are second generation HIV non-nucleoside reverse transcriptase inhibitors(NNRTIs) with enhanced potency. Efavirenz (Sustiva TM) has approved for the treatment of HIV (*Antimicrob. Agents Chemother.* **1995**, 39, 2602). DPC083 and DPC 961 are currently undergoing clinical evaluation (*Journal of Medicinal Chemistry* vol.43, no.10, **2000**, 2019-2030).

Some methods have been reported for the synthesis of Efavirenz (Sustiva TM) (*Angew. Chem. Int. Ed.* no. 5, **1999**, 711-713; *Journal of Organic Chemistry* vol.63, no.23, **1998**, 8536-8543), DPC083 and DPC 961. These prior methods prepared DPC 961 by a fractional crystallization or 1,4-diastereoselective addition protocol , both employing auxiliary (*Journal of Organic Chemistry* vol.68, no.3, **2003**, 754-761; *Tetrahedron Letter* vol.41, **2000**, 3015-3019). Very recently, *WO0170707* disclosed an asymmetric processe for preparing DPC961 via chiral ligand mediated asymmetric addition. However, in this process large excess strong base (lithium alkyl and LHMDs) and excess chiral ligand was used under very strict condition (-20°C).

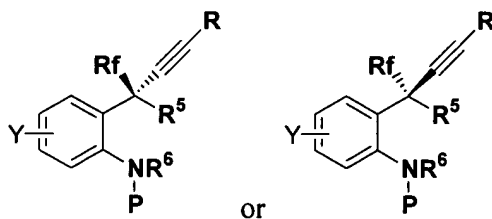
Disclosure of the invention

The present invention relates to a new process of asymmetric alkynylation of ketone or ketimine. The invention also provide the new amino alcohol ligand used in the alkynylation process.

A new process of asymmetric alkynylation of ketone or ketimine is disclosed, involving the enantioselective addition of terminal alkynes to a trifluoromethyl ketone or ketimine intermediate to give a chiral tertiary proparglic alcohols or amines. The adduct compounds are the key precursors to the potent HIV reverse transcriptase inhibitor Efavirenz (DMP 266), DPC 961 and DPC 083 . This was achieved by direct installation of the quaternary carbon atom of Efavirenz (Sustiva TM) , DPC083 and DPC 961 with absolute stereo controlling by chiral addition of zinc or copper acetylide to a ketone or ketimine intermediate to give a proparglic alcohol or amine, with enantiomeric excess up to 99%.

Further, it is unexpected that reaction of zinc or copper acetylide with a trifluoromethyl ketone or ketimine produces an optically active product. In the present invention, this is achieved with a new chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The unusually high levels of optical activity (up to 99% ee) and very mild reaction condition make the method advantageous and practical. The chiral ligand can also be recycled.

In this invention, there is disclosed a process which uses an amino alcohol ligand as catalyst for the asymmetric synthesis of the chiral compound of the structure

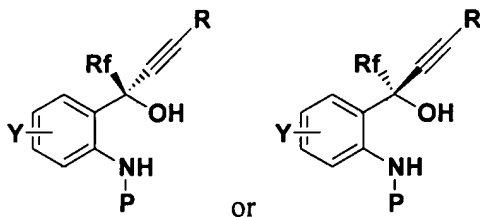


where Y is H, mono or multisubstituted electronwithdrawing group or electron-donating group, preferred is H, mono or di-substituted electronwithdrawing group or electron-donating group, wherein Y can be located at *m*-,*o*-,or *p*-position of the benzene ring; More preferably, Y is H, Cl, Br, CH₃SO₂, CH₃CH₂SO₂, NO₂ or F. Most preferably, Y is F, Cl, Br; P is hydrogen or an amino protecting group;

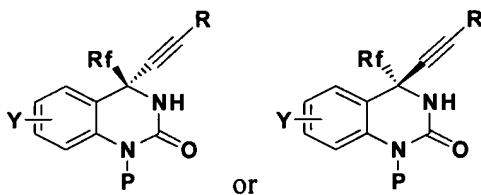
R_f is fluoro-containing alkyl, preferred is C₁~C₂₀ fluoro-containing alkyl, more preferred is C₁~C₄ fluoro-containing alkyl;

R is trialkylsilyl, alkyl, cycloalkyl or aryl group;

R⁶ is hydrogen when R⁵ is hydroxy, of the structure:

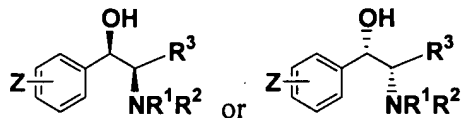


Also R⁵ and R⁶ can be cyclization such as -HNCO- of the structure



where Y, P, R, R_f is the same as above.

The above amino alcohol ligand is of the structure



wherein R¹, R² is amino protecting group, R¹, R² is the same or different group,

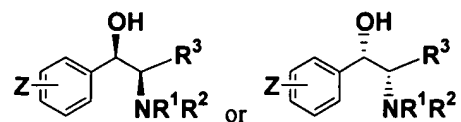
R³ is alkyl, substituted alkyl (substituted group can be alkyloxy or silyloxy, especially), carboxylic group, carbalkoxy group, hydroxy methyl, cycloalkyl, aryl or CH₂OR⁴; wherein R⁴ is an oxygen protecting group,

Z is H, mono or multisubstituted electronwithdrawing group or electron-donating group, preferred is H, mono or di-subsubstituted electronwithdrawing group or electron -donating group, wherein Z can be located at *m*-, *o*-, or *p*-positon of the benzene ring; More preferable is H, F, Cl, Br, I, CH₃SO₂ OH, PhCH₂O, AcO, MeO, EtO, Me₂NCH₂CH₂O, Et₂NCH₂CH₂O, PhCH₂OCO, *t*-Bu, *i*-Pr, NH₂, or NO₂;

The process Comprising the steps of:

(a) providing a mixture of chiral ligand (1R, 2R)-2-*N,N*-substituted-1-(substituted

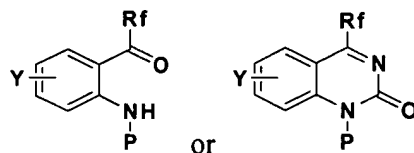
-phenyl)-2- R^3 -substituted-2-aminoethanol or its enantiomer, of the structure



wherein R^1 , R^2 , R^3 , Z is the same as above;

with a terminal alkyne and a Zn(II), Cu(II) or Cu(I) salts in the presence of an organic base in organic solvent, wherein the terminal alkyne is $H-C\equiv C-R$, R is the same as above.

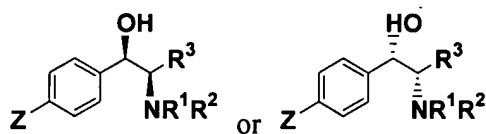
(b) mixing with the mixture of step (a) of reactant of the structure



wherein P, Rf, Y is the same as above;

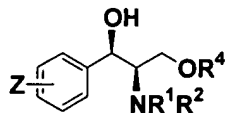
In an preferred embodiment, quenching the above reaction by adding a proton source, to give the desired compound. Preferable proton source is NH_4Cl aqueous (sat.), water, hydrochloric acid or citric acid aqueous.

In an embodiment, the amino alcohol ligand is a compound of the structure



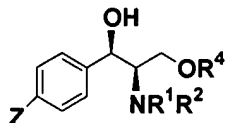
wherein R^1 , R^2 , R^3 , Z is the same as above.

In another embodiment, the chiral ligand is a compound of the structure or its enantiomer



wherein R^1 , R^2 , R^4 , Z is the same as above.

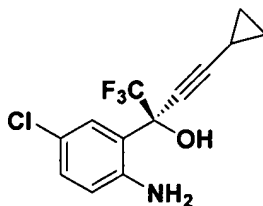
In another embodiment, the chiral ligand is a compound of the structure or its enantiomer



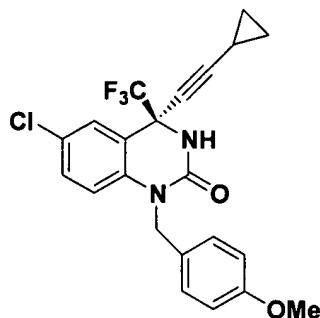
wherein R^1 , R^2 , R^4 , Z is the same as above.

In an embodiment, this invention provides a novel process for making a compound of

the structure or its enantiomer

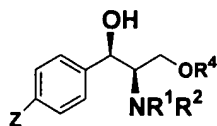


or of the structure or its enantiomer



Comprising the steps of:

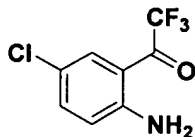
(a) providing a mixture of 0.1~3 molar equivalent of a chiral ligand (1R, 2R)-2-*N,N*-substitutedamino-1-(4-substituted-phenyl)-3-*O*-substituted-propane-1-ol, of the structure or its enantiomer,



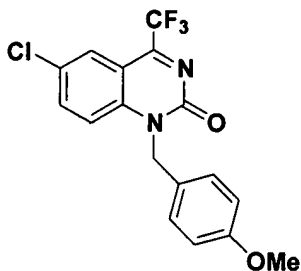
wherein Z, R¹, R², R⁴ is the same as above,

with 0.1~3 molar equivalent of a terminal alkyne and 0.1~3 molar equivalent of Zn(II), Cu(I) or Cu(II) salts in the presence of 1~4 molar equivalent of an organic base in organic solvent, the terminal alkyne is $\text{H}-\text{C}\equiv\text{C}-\text{Cyclopropyl}$;

(b) mixing with the mixture of step (a) of 1.0 molar equivalent of reactant of the structure



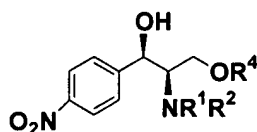
or of the structure that is the 4-methoxybenzyl protected ketimine(I):



(I)

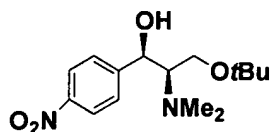
preferably, maintaining the resulting reaction mixture at a temperature of between about 0-50°C, especially at room temperature for 1-20hr; quenching by adding a proton source to give the desired compound.

In another embodiment, the chiral ligand is a compound of the structure or its enantiomer

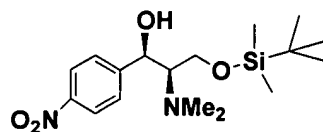


wherein R¹, R², R⁴ is the same as above; preferably, R¹, R² is Me.

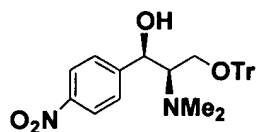
In another preferred embodiment, the chiral ligand is a compound of the structure or its enantiomer



In another preferred embodiment, the chiral ligand is a compound of the structure or its enantiomer



In another preferred embodiment, the chiral ligand is a compound of the structure or its enantiomer



In another embodiment, wherein the stoichiometric ratios are about 0.1- 3 equivalent molar

of ligand to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5- 3 equivalent molar of ligand to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of ligand to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.1- 3 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5- 3 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another embodiment, the metal salts is selected from ZnCl_2 , ZnBr_2 , ZnF_2 , ZnI_2 , Zn(OTf)_2 , $\text{Zn(SO}_3\text{CF}_2\text{H)}_2$, CuCl_2 , CuBr_2 , Cu(OTf)_2 , CuCl , CuBr , Cu(OTf) , CuI .

In another preferred embodiment, the Zinc(II) or Cu(II) salts is Zn(OTf)_2 or Cu(OTf)_2 .

In another preferred embodiment, the Zinc(II) is Zn(OTf)_2 .

In another embodiment, wherein the stoichiometric ratios are about 0.1-3 equivalent molar of the Zinc(II) salt or Cu salt to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5-3 equivalent molar of the Zinc(II) salt or Cu salt to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of the Zinc salt or Cu salt to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 1.0-4.0 equivalent molar of the organic base to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 2.0~3.5 equivalent molar of the organic base to substrate ketone or ketimine.

In another embodiment, wherein the organic base is selected from $\text{MeN}(i\text{Pr})_2$, HNEt_2 , $\text{N}(i\text{Pr})_3$, pyridine, NEt_3 , piperidine, NBu_3 , $\text{EtN}(i\text{Pr})_2$.

In another preferred embodiment, wherein the organic base is NEt_3 .

In another embodiment, the reaction is carried out in aprotic solvent or ethereal solvent.

Examples of aprotic solvent include THF, dioxane, CH_2Cl_2 , Et_2O , benzene, DME, toluene, *n*-hexane, and cyclohexane, or mixture thereof.

In another preferred embodiment, solvent is toluene.

In another embodiment, wherein the reaction temperature is between about 0 °C and about 100 °C.

In another preferred embodiment, wherein the reaction temperature is between about 0°C and about 50 °C, especially at room temperature.

In another embodiment, wherein R^1 and R^2 is alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl protected groups, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, $\text{C}_1\sim\text{C}_3$ hydroxy alkyl, $\text{C}_1\sim\text{C}_4$ alkyl, $\text{C}_1\sim\text{C}_3$ alkoxy, CN; or R^1 , R^2 can be $-(\text{CH}_2)_n\text{X}(\text{CH}_2)_m-$, where X can be CH_2 , O or NH; n, m is an integer from 1 to 6.

P is hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl protected groups, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, $\text{C}_1\sim\text{C}_3$ hydroxyalkyl, $\text{C}_1\sim\text{C}_4$ alkyl, $\text{C}_1\sim\text{C}_3$ alkoxy, CN;

R^4 is alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, $\text{C}_1\sim\text{C}_3$ hydroxy alkyl, $\text{C}_1\sim\text{C}_4$ alkyl, $\text{C}_1\sim\text{C}_3$ alkoxy, CN;

electronwithdrawing group is halogen, NO_2 , CF_3 , CH_3SO_2 , $\text{CH}_3\text{CH}_2\text{SO}_2$, PhCH_2OCO , or AcO . electron-donating group is alkoxy (especially $\text{C}_1\sim\text{C}_3$ alkoxy), OH, $\text{Me}_2\text{NCH}_2\text{CH}_2\text{O}$, $\text{Et}_2\text{NCH}_2\text{CH}_2\text{O}$, NH_2 , alkyl (especially $\text{C}_1\sim\text{C}_4$ alkyl).

In another preferred embodiment, wherein R^1 and R^2 is $\text{C}_1\sim\text{C}_{20}$ alkyl, $\text{C}_1\sim\text{C}_{20}$ substituted alkyl, benzyl, substituted benzyl or $\text{C}_1\sim\text{C}_{20}$ trialkylsilyl protected groups, the substituted group is the same as above; or R^1 , R^2 can be $-(\text{CH}_2)_n\text{X}(\text{CH}_2)_m-$, where X can be CH_2 , O or NH; n, m is an integer from 1 to 6.

P is hydrogen, $\text{C}_1\sim\text{C}_{20}$ alkyl, $\text{C}_1\sim\text{C}_{20}$ substituted alkyl, benzyl or substituted benzyl or $\text{C}_1\sim\text{C}_{20}$ trialkylsilyl protected groups, the substituted group is the same as above;

R is $\text{C}_1\sim\text{C}_{20}$ trialkylsilyl, $\text{C}_1\sim\text{C}_{20}$ alkyl, $\text{C}_3\sim\text{C}_{20}$ cycloalkyl or aryl, the aryl is phene, naphthalene, furan, thiophene, pyrrole.

R³ is C₁~C₂₀ alkyl; C₁~C₂₀ alkyl substituted with alkyloxy or silyoxy, carboxylic group, C₁~C₂₀ carbalkoxy group, hydroxyl methyl, C₃~C₂₀ cycloalkyl, aryl or CH₂OR⁴, wherein R⁴ is C₁~C₂₀ alkyl, C₁~C₂₀ substituted alkyl, benzyl or substituted benzyl or C₁~C₂₀ trialkylsilyl, the substituted group is the same as above.

Z is H, F, Cl, Br, I, CH₃SO₂ OH, PhCH₂O, AcO, MeO, EtO, Me₂NCH₂CH₂O, Et₂NCH₂CH₂O, PhCH₂OCO, *t*-Bu, *i*-Pr, NH₂, or NO₂;

Y is H, F, Cl, Br, I, CH₃SO₂ OH, PhCH₂O, AcO, MeO, EtO, Me₂NCH₂CH₂O, Et₂NCH₂CH₂O, PhCH₂OCO, *t*-Bu, *i*-Pr, NH₂, or NO₂;

In another preferred embodiment, wherein R¹ and R² is C₁~C₄ alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C₁-C₄ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or N-trialkylsilyl groups; or R¹, R² can be -(CH₂)₂O(CH₂)₂-, -(CH₂)₂N(CH₂)₂-, -(CH₂)₅- or -(CH₂)₆-.

P is hydrogen, C₁~C₄ alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C₁~C₄ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl;

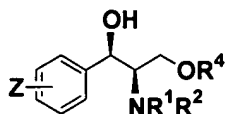
R is C₁~C₄ alkyl, C₃~C₆ cycloalkyl or aryl, the aryl is phenyl, naphthalene, furan, thiophene, pyrrole.

R³ is C₁~C₄ alkyl; C₁~C₄ alkyl substituted with alkyloxy or silyoxy, carboxylic group, C₁~C₄ carbalkoxy group, hydroxyl methyl, C₃~C₆ cycloalkyl, aryl or CH₂OR⁴, wherein R⁴ is C₁~C₄ alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C₁~C₄ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl;

Y is H, Cl, Br, CH₃SO₂-, CH₃CH₂SO₂-, NO₂ or F;

Halogen or halo is fluoro, chloro, bromo and iodo.

In this invention, there is also disclosed a novel chiral ligand of the structure or its enantiomer



wherein R^1, R^2 is amino protecting group, R^1, R^2 is the same or different group,

R^4 is oxygen protecting group,

Z is mono or multisubstituted electronwithdrawing group or electron-donating group, wherein Z can be located at *m*-,*o*-, or *p*-position of the benzene ring.

Preferably, R^1 and R^2 is alkyl, substituted alkyl, benzyl, substituted benzyl, or trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2 , O or NH ; n, m is an integer from 1 to 6.

R^4 is alkyl, substituted alkyl, benzyl, substituted benzyl, or trialkylsilyl group; Example of the substituted group of alkyl or benzyl is phenyl, naphthyl, halogen, hydroxy, NO_2 , $C_1 \sim C_3$ alkoxy, CN;

Z is halogen, NO_2 , CF_3 , CH_3SO_2 , $CH_3CH_2SO_2$, CH_3O , OH or alkyl;

Preferably, Z is mono or multisubstituted electronwithdrawing group or electron-donating group, more preferably Z is F, Cl, Br, I, CH_3SO_2 , OH, $PhCH_2O$, AcO, MeO, EtO, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, $PhCH_2OCO$, *t*-Bu, *i*-Pr, NH_2 , or NO_2

More preferably, R^1, R^2 is $C_1 \sim C_{20}$ alkyl, $C_1 \sim C_{20}$ substituted alkyl, benzyl, substituted benzyl, $C_1 \sim C_{20}$ trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2 , O or NH ; n, m is an integer from 1 to 6.

R^4 is $C_1 \sim C_{20}$ alkyl, $C_1 \sim C_{20}$ substituted alkyl, benzyl, substituted benzyl, or $C_1 \sim C_{20}$ trialkylsilyl group ;

Most Preferably, R^1, R^2 is $C_1 \sim C_4$ alkyl (such as methyl), benzyl unsubstituted or substituted with $C_1 \sim C_4$ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2N(CH_2)_2-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

R^4 is $C_1 \sim C_4$ alkyl (such as butyl), benzyl unsubstituted or substituted with $C_1 \sim C_4$ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl group which exclude *t*-Butyldimethylsilyl.

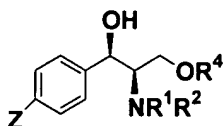
Z is Cl, Br, NO₂, CF₃, CH₃SO₂, CH₃CH₂SO₂, CH₃O, OH or C₁~C₄ alkyl, especially Z is CH₃SO₂ or NO₂;

and when Z is NO₂ at 4-position of the phenyl, R¹ is N=O, R² is COCH₃, R⁴ is only alkyl, substituted alkyl, benzyl, substituted benzyl, or trialkylsilyl;

and when Z is NO₂ at 4-position of the phenyl, R¹, R² is CH₃, the ligand is only (1R, 2R)-2-*N,N*-dimethylamino-1-(4-nitrophenyl)-3-*O*-R⁴-1-ol;

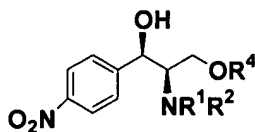
and when Z is OCH₃ at 4-position of the phenyl, R¹, R² is CH₃, R⁴ is only alkyl, substituted alkyl, benzyl, substituted benzyl; said substituted group is the same as above;

In another embodiment, the novel chiral ligand is a compound of the structure or its enantiomer



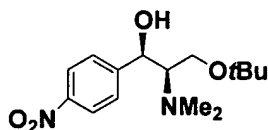
R¹, R², R⁴, Z is the same as above.

In another embodiment, the novel chiral ligand is a compound of the structure or its enantiomer

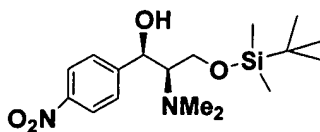


R¹, R², R⁴ is the same as above, preferably, R¹, R² is Me.

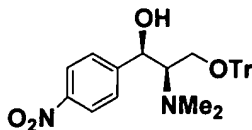
In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enantiomer



In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enantiomer



In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enantiomer



As used herein except where noted, “alkyl” is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; if the number of carbon atoms is unspecified, “alkyl” is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon atoms, both branched and straight-chain saturated aliphatic hydrocarbon groups. For example, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl.

“Halogen” or “halo” as used herein, means fluoro, chloro, bromo and iodo.

“alkoxy” is intended to include both branched- and straight-chain groups having the specified number of carbon atoms; if the number of carbon atoms is unspecified, “alkoxy” is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon atoms.

If the number of carbon atoms is unspecified, “cycloalkyl” is intended to include 3 to 20 carbon atoms, preferred is 3 to 6 carbon atoms.

“aryl” is intended to include phenyl, naphenyl, furan, thiophene, pyrrole, preferred is phenyl.

“carbalkoxy group” is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon

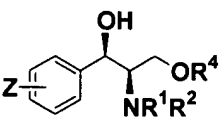
In the processes of this present invention, R^1 and R^2 is the same or different group. R^1 and R^2 is any suitable amino protecting group, and includes, but is not limited to, alkyl, substituted alkyl (the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, $C_1\sim C_3$ hydroxy, alkyl, $C_1\sim C_3$ alkoxy, CN), benzyl, substituted benzyl (the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, $C_1\sim C_3$ hydroxy, alkyl, $C_1\sim C_3$ alkoxy) or trialkylsilyl, or R^1 , R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2 , O or NH ; n, m is an integer from 1 to 6. Examples of R^1 or R^2 is $C_1\sim C_4$ alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with $C_1\sim C_{20}$ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl;

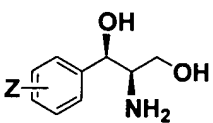
para-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; preferred is C₁-C₄ alkyl, benzyl unsubstituted or substituted with C₁-C₄ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or R¹, R² can be -(CH₂)₂O(CH₂)₂-, -(CH₂)₂N(CH₂)₂-, -(CH₂)₅- or -(CH₂)₆-. Other protective groups are according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999, pp. 494-653. A preferable amino protecting group is *para*-methoxybenzyl.

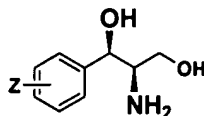
P is hydrogen or any suitable amino protecting group described as above.

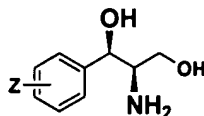
In the processes of this present invention, R⁴ is any suitable oxygen protecting group, and includes, but is not limited to, alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl protected groups. Preferred is C₁-C₂₀ alkyl unsubstituted or substituted, benzyl unsubstituted or substituted, or trialkylsilyl protected groups. The substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, CN. Examples of R³ is C₁-C₄ alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C₁-C₄ alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl groups. Other protective groups are according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999, pp. 17-245. A preferable oxygen protecting group is *t*-butyl.

In the processes of this present invention, electronwithdrawing group includes, but is not limited to, halogen, NO₂, CF₃, CH₃SO₂, CH₃CH₂SO₂, PhCH₂OCO or AcO. Electron-donating group includes, but is not limited to, alkoxy especially C₁-C₂₀ alkoxy, OH, Me₂NCH₂CH₂O, Et₂NCH₂CH₂O, NH₂, alkyl.

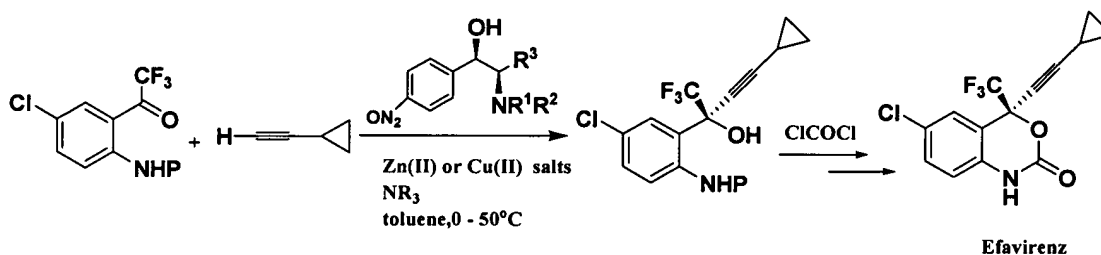
The synthesis of the chiral ligand  or its enantiomer is based on the

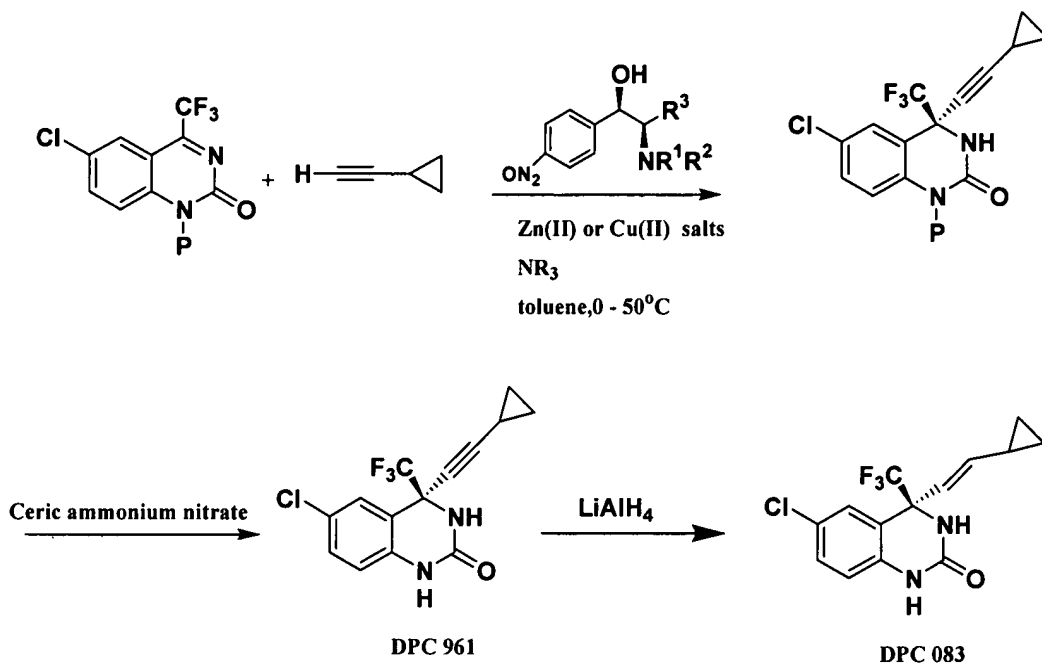
simple and short modification of  or its enantiomer. The hydroxy group at 3-position and amino at 2-position group was protected according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999.



For example, the amino group at 2-position of  can be protected first by condensation of corresponding aldehyde then by reducing in organic solvent. Example of the reductant can be formic acid, NaBH₄, KBH₄, LiAlH₄ or Pd/C. The amino group at 2-position also can be protected by reaction with R¹X or R²X in organic solvent in the presence of base, wherein X is halogen. The hydroxy group at 3-position can be protected with *t*-butyl by reaction with iso-butene catalyzed by acid. The hydroxy group at 3-position also can be protected with R³ by reaction with R³X, wherein X is halogen. The above reaction condition can be routine. Said base can be inorganic base or organic base, for example, K₂CO₃, Na₂CO₃, NaOH, KOH or NEt₃. Example of said organic solvent can be alcohol, alkyl substituted by halogen or ether. Example of the protection detail is refluxing with formaldehyde and formic acid to protect amino group with di-methyl, or reacting with benzaldehyde for condensation and then reducing by NaBH₄ to protect the amino group by benzyl group.

Efavirenz, DPC 961 and DPC 083 can be synthesized by the following method.





The present invention provided a novel ligand. The use of the ligand relates to asymmetric addition particularly to a direct synthesis of the optically active DPC 961, DPC083 and efavirenz, by chiral addition of zinc or copper acetylide to a ketimine intermediate to give a propargylic amine, with enantiomeric excess up to 99%; or by chiral addition of zinc or copper acetylide to an ketone intermediate to give a propargylic alcohol.

Compared with the prior methods of preparation DPC 961, the process of this invention achieved with a chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The prior methods by a derivatization and fractional crystallization or 1, 4-diastereoselective addition protocol, both employing auxiliary (*Journal of Organic Chemistry* vol.68, no.3, 2003, 754-761; *Tetrahedron Letter* vol.41, 2000, 3015-3019). WO 200170707 disclosed a asymmetric processes for preparing DPC961 via chiral moderated asymmetric addition. However, in this process large excess strong base (lithium alkyl and LHMDs) and excess chiral ligand was used under very strict condition (-20°C), while the process of this invention can be performed with very mild reaction condition (20-40°C). The ligand used in the reaction is less expensive, further more it can be recycled. The workup is also very simple. All of this will reduced the cost of the process greatly.

Further, it is unexpected that reaction of zinc or copper acetylide with a trifluoromethyl

ketimine produces an optically active product. The invention not only provide a kind of novel ligand in the enantioselective alkynylation of ketimine, but also provide a practical industrial process of preparation DPC 961. In the present invention, this is achieved with a chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The unusually high levels of optical activity (up to 99% ee) and very mild reaction condition make the method advantageous and practical.

Best Mode for Carrying Out the Invention

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

Example 1

Preparation of (1R, 2R)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane -1,3-diol:

See reference Jiang, B.; Chen, Z. L.; Tang, X. X. *Org. Lett.* **2002**, 4, 3451.

Example 2

Preparation of (1R, 2R)-3-(*t*-butyloxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol: Concentrated H₂SO₄ (0.8g) was added dropwise to a solution of (1R, 2R)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol(1.8 g, 7.5 mmol) in CH₂Cl₂ (20 mL) at 0-5 °C. Isobutene gas was bubbled for 1h with the temperature maintained at 0-5 °C. Concentrated H₂SO₄ (0.2 g) was added dropwise, the mixture was allowed to warm to room temperature and was stirred vigorously for 5-7 hrs with the isobutene bubbling into. Then the mixture was cooled to 0-5°C and washed with K₂CO₃ (sat). The organic layer was dried with Na₂SO₄ and concentrated *in vacuo*. Purified by flash chromatography on silica gel afforded the ligand (1.44 g, 65%). (Hexane: EtOAc = 1:1). mp 100.0 – 101.3 °C; $[\alpha]_D^{20} = +23.5$ (c, 1.00, CHCl₃); FTIR (KBr) 3333, 2972, 1606, 1523, 1357, 1197, 861 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 9.9 Hz, 1H), 3.34 (dd, *J* = 3.0 Hz, and 9.9 Hz, 1H), 3.21 (dd, *J* = 6.5 Hz, and 10 Hz, 1H), 2.56 (m, 1H), 2.47 (s, 6H), 1.06 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 150.6, 147.6,

128.46, 123.49, 73.3, 70.3, 69.8, 56.0, 41.8, 27.4; MS (EI) m/e 223(M^+-73 , 3), 209 (21), 144 (68), 88 (100), 71(10), 57(31); Anal. calcd. for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11; N, 9.46. Found: C, 60.72; H, 8.26; N, 9.14.

Example 3

Preparation of (1R, 2R)-3-(*t*-butyldimethylsilyloxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol:

(1R, 2R)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.946 g, 8.1 mmol) was dissolved in CH_2Cl_2 (30 mL), TBDMSCl (1.28g, 5.3 mmol) and imidazole (1.4 g, 20.6 mmol) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 2.72 g product. FTIR (KBr) 3344, 2954, 1606, 1525, 1349 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.25-8.20 (d, J = 8.5 Hz, 2H), 7.6-7.55 (d, J = 8.5 Hz, 2H), 4.65 (d, J = 9.7 Hz, 1H), 3.77-3.6(dd, J = 11.3 Hz, 2.7 Hz 1H), 3.5-3.45(dd, J = 11.3 Hz, 6.0 Hz, 1H), 2.50 (m, 7H), 1.85 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 147.4, 128.0, 123.3, 69.0, 57.1, 41.6, 25.7, 17.9, -5.9; MS (EI) m/e 297(M^+-57 , 0.3), 209 (8.2), 202(100). Anal. calcd. for $C_{17}H_{30}N_2O_4Si$: C, 57.60; H, 8.53; N, 7.90. Found: C, 57.82; H, 8.18; N, 7.77.

Example 4

Preparation of (1R, 2R)-3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl) propane-1-ol:

(1R, 2R)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol(1.946 g, 8.1 mmol) was dissolved in CH_2Cl_2 (50 mL), Triphenylmethane chloride (TrCl) (3.34 g, 12 mmol) and Et_3N (2 mL) was added at 0°C. The mixture was stirred for overnight at rt. Work up to give 3.7 g product. FTIR (KBr) 3344, 2954, 1606, 1525, 1349 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.09-8.06 (d, J = 8.4 Hz, 2H), 7.36-7.33 (d, J = 8.6 Hz, 2H), 7.25-7.17 (m, 15H), 4.27 (d, J = 10.0 Hz, 1H), 3.28(dd, J = 10.2 Hz, 6.4 Hz, 1H), 3.01(dd, J = 10.7 Hz, 3.9 Hz, 1H), 2.71 (m, 1H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 147.6, 143.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.3, 123.7, 87.7, 70.9, 70.6, 58.6, 41.6.

Example 5

Preparation of (1R, 2R)-2-*N*-benzyl-2-*N*-methylamino-3-(*p*-nitrophenyl)propane-1,3-diol:

(1R, 2R)-2-aminol-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol) and benzaldehyde (1.2 g, 10.5 mmol) was added to methanol (10 mL), then CuSO₄ (0.2 g) was added to the mixture. The mixture was refluxed for 7 hr, cooled to rt and filtered. To the filtrate was added THF (10 mL). NaBH₄ (0.4 g) was added slowly. The resulting mixture was refluxed for 2 hr and cooled. 5% HCl was added to acidified the solution. Extracted with ether and concentrated. The residue mixture was refluxed with HCHO(10 mL) and HCOOH(10 mL) for 8hr. The mixture was cooled and nutralized with NaOH. Extracted with CH₂Cl₂ and dried with NaSO₄. After purification give 1.2 g product.

Example 6

Preparation of (1R, 2R)-3-(*t*-butyldimethylsilyloxy)- 2-*N*-benzyl-2-*N* -methylamino-1-(*p*-nitrophenyl) propane-1-ol

(1R, 2R)-2-*N*-benzyl-*N*-methylamino-3-(*p*-nitrophenyl)propane-1,3-diol (632 mg) was dissolved in CH₂Cl₂ (15 mL), TBDMSCl (300 mg, 2 mmol) and imidazole (136 mg, 2 mmol) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 600 mg proguet. FTIR (KBr) 3344, 2972, 1606, 1525,1348 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.38-7.31 (m, 5H), 4.70 (d, *J* = 9.6 Hz, 1H), 4.04 (d, *J* = 13.0 Hz, 1H), 3.77-3.55(m, 3H), 2.70 (m, 1H), 2.43 (s, 3H), 0.90 (s, 9H), 0.01 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 150.6, 147.6, 138.46, 129.2, 128.8, 128.4, 127.7, 123.69, 70.3, 69.8, 60.1, 58.0, 37.5, 26.0, 18.3, -5.4; MS (EI) *m/e* 415(M⁺-15, 0.9), 278 (100), 91(73);

Example 7

Preparation of (1R, 2R)-3-(triphenylmethoxy)-2-*N*-benzyl-2-*N*-methylamino-1-(*p*-nitrophenyl) propane-1-ol:

(1R, 2R)-2-*N*-benzyl-*N*-methylamino-3-(*p*-nitrophenyl)propane-1,3-diol (380 mg, 1.2 mmol) was dissolved in CH₂Cl₂ (15 mL), TrCl (334 mg, 1.2 mmol) and Et₃N (0.2 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 500 mg product. mp 58.0 – 59.3 °C; FTIR (KBr) 3314, 2926, 1602, 1521, 1346 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.40-7.19 (m, 22H), 4.30 (d, *J* = 9.6 Hz, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.73 (d, *J* = 6.8 Hz, 1H), 3.36 (m, 1H), 3.06 (m, 1H) 2.89 (m, 1H), 2.33 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 150.6, 147.6, 143.46, 138.2, 129.3, 128.8, 128.7, 128.6, 128.4, 128.0, 127.7, 127.4, 123.7, 87.8, 70.5, 69.8, 60.1, 58.0, 37.0; MS (EI) *m/e* 406 (M⁺-152, 24.9), 243 (100); Anal. calcd. for C₁₅H₂₄N₂O₄: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.26; H, 6.06; N, 4.65.

Example 8

Preparation of (1R, 2R)-3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(phenyl)propane-1-ol:

(1R, 2R)-2-*N,N*-dimethylamino-3-(phenyl)propane-1,3-diol (1.95 g, 10 mmol) was dissolved in CH₂Cl₂ (50 mL), Triphenylmethane chloride (TrCl) (3.33 g, 12 mmol) and Et₃N (2 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 4.0 g product. FTIR (KBr) 3344, 2954, 1609, 1525, 1349 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.06 (m, 20H), 4.87 (d, *J* = 10.0 Hz, 1H), 3.76 (dd, *J* = 10.2 Hz, 6.4 Hz 1H), 3.51 (dd, *J* = 10.7 Hz, 3.9 Hz 2H), 2.80 (m, 1H), 2.38 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 143.6, 138.9, 128-129 (16 C), 125.7-126.6 (4 C), 84.9, 72.9, 68.6, 69.6, 49.6, 39.6.

Example 9

Preparation of (1R, 2R)-3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(*p*-methylsulphonylphenyl)propane-1-ol:

(1R, 2R)-2-*N,N*-dimethylamino-3-(*p*-methylsulphonylphenyl)propane-1,3-diol (5.46 g, 20 mmol) was dissolved in CH₂Cl₂ (80 mL), Triphenylmethane chloride (TrCl) (6.8 g, 25 mmol) and Et₃N (4 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 9.10 g product. FTIR (KBr) 3344, 2954, 1609, 1525, 1349 cm⁻¹; ¹H NMR (300

MHz, CDCl₃) δ 7.48-7.40 (d, J = 8.4 Hz, 2H), 7.27-7.19 (d, J = 8.6 Hz, 2H), 7.12-7.04 (m, 15H), 4.86(d, J = 10.0 Hz, 1H), 3.72 (dd, J = 10.2 Hz, 6.4 Hz 1H), 3.56(dd, J = 10.2 Hz, 6.4 Hz 2H), 2.94(s, 3H), 2.81(m, 1H), 2.38(s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 143.8, 143.0, 138.6, 135.0, 129-126(16C), 84.9, 72.9, 69.6, 68.0, 49.6, 41.0, 39.6.

Example 10

Preparation of (1R, 2R)-2-*N*-prrolidinyl-3-(*p*-nitrophenyl)propane-1,3-diol:

(1R, 2R)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol) dissolved in DMF (10 mL), anhydrous K₂CO₃ (3.15 g, 22 mmol) was added at 0-5 °C. 1,4-dibromobutane (2.4 g, 11 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred vigorously for 35 h. After filtration, the solution was added to water and extracted with EtOAc. Purified to give the product 2.2 g (83%) as an yellow oil. FTIR (neat) 3393, 2969, 1605, 1521, 1348cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 4.63 (d, J = 8.1 Hz, 1H), 3.80 (br, 2H), 3.56 (m, 2H), 2.81-2.70 (m, 5H), 1.79-1.68 (m, 4H); MS (ESI) m/e 267(M⁺+1).

Example 11

Preparation of (1R, 2R)-3-(*t*-butyldimethylsilyloxy)-2-*N*-prrolidinyl-1-(*p*-nitrophenyl)propane-1-ol:

(1R, 2R)-2-*N*-prrolidinyl-3-(*p*-nitrophenyl)propane-1,3-diol (2.66 g, 10 mmol) was dissolved in CH₂Cl₂ (80 mL). After cooled to 0-5 °C, imidazole (680 mg, 10 mmol) was added. TBDMSCl (1.65 g 11 mmol) was added in three portions. The mixture was allowed to warm to room temperature and was stirred for 5h. After workup to give 3.0 g (79%) yellow oil as product. FTIR (neat) 3346, 2937, 2924, 2858, 1604, 1525, 1347cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.9 Hz, 2H), 4.70 (d, J = 8.5 Hz, 1H), 3.65 (dd, J = 4.0 Hz, and 11.0 Hz, 1H), 3.52 (dd, J = 5.3 Hz, and 10.8 Hz, 1H), 2.82-2.71 (m, 5H), 1.83-1.73 (m, 4H), 0.85 (s, 9H), -0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 150.8, 147.2, 127.7, 123.2, 69.8, 67.4, 58.2, 49.2, 25.7, 23.4, 17.9, -5.8; MS (ESI) m/e 381(M⁺+1).

Example 12

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O-t*-butylpropane-1-ol (2.96 g, 0.2 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) and 4-chloro-2-trifluoroacetyl aniline (1.74 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (75% yield, 99.3% ee).

Example 13

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O-t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline (2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (60% yield, 90.1% ee).

Example 14

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O-t*-butylpropane-1-ol (2.96 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to

the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline(2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (60% yield, 99.1% ee).

Example 15

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (354 mg, 1 mmol) and Zn(OTf)₂ (0.36 g, 1 mmol) was dissolved in toluene (2 mL) at 25°C. NEt₃ (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat *t*-butylacetylene (1.3 mL, 12 mmol) was added to the mixture. The 4-chloro-2-trifluoroacetyl aniline (2.3 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding 1N HCl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (85% yield, 94.1%ee).

Example 16

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-benzyl-*N*-methyamino-1-(4-nitrophenyl)-3-*O*-tritylpropane-1-ol (558 mg, 1 mmol) and Cu(OTf)₂ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25°C. NEt₃ (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat phenylacetylene (1.1 mL, 12 mmol) was added to the mixture. The 4-chloro-2-trifluoroacetyl aniline (2.3 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was

collected by filtration, and dried to give the adduct product (67% yield, 55%ee).

Example 17

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-methyl-2-*N*-benzyl-*N*-methylamino-1-phenyl-ethane-1-ol (2.55 g, 10.0mmol) and Zn(OTf)₂ (3.6 g, 10.0mmol) was dissolved in toluene (10mL) at 25°C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline (2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25°C for 10hr. The resulting solution was quenched by adding NH₄Cl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (51% yield, 96.1% ee).

Example 18

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25°C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 99.3% ee).

Example 19

Preparation of the DPC961

The *p*-methoxybenzyl protected DPC 961 (2 mmol) was dissolved in 10% aqueous CH₃CN (10 mL), and ceric ammonium nitrate (4.4 g, 8 mmol) was added. After stirring for 4 hr at 25 °C, the reaction was diluted with water and extracted with EtOAc. The combined organic layer was concentrated *in vacuo* to afford DPC 961 in 80% yield.

Example 20

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (72% yield, 99.1% ee).

Example 21

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (4.82 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers were dried with Na₂SO₄ and

concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (76% yield, 98.0% ee).

Example 22

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (5.58 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25°C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated NH₄Cl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (80% yield, 51.0% ee).

Example 23

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (5.58 g, 10 mmol) and Cu(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (68% yield, 98.0% ee).

Example 24

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (354 mg, 1 mmol) and Zn(OTf)₂ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25°C. NEt₃ (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (75% yield, 98.1% ee).

Example 25

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (558 mg, 1 mmol) and Cu(OTf)₂ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (67% yield, 45% ee).

Example 26

Addition of *t*-butylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-

(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25°C. HN*i*Pr₂ (2.0 mL) was added. After 1 hr, the neat *t*-butylacetylene (1.3 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (45% yield, 96.5% ee).

Example 27

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1*R*, 2*R*)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 kg, 10 mol) and Zn(OTf)₂ (3.6 kg, 10 mol) was dissolved in toluene (10 L) at 25 °C. NEt₃ (2.0 L, 15 mol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 L, 12 mol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 kg, 10 mol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (90.9% yield, 99.1% ee).

Example 28

Addition of phenylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1*R*, 2*R*)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in THF (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat phenylacetylene (1.1 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl

protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (91% yield, 99.0% ee).

Example 29

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 50 °C for 2 hr and then cooled to 25 °C. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (81% yield, 97.1% ee).

Example 30

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethylamino-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and ZnBr₂ (2.3 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 50 °C for 2 hr and then cooled to 25 °C. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25

°C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (31% yield, 63.1% ee).

Example 31

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethylamino-1-(4-nitrophenyl)-2-*t*-butyloxycarbonyl-ethane-1-ol (3.1 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 99.3% ee).

Example 32

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethylamino-1-(4-nitrophenyl)-2-hydroxycarbonyl-ethane-1-ol (2.5 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was

collected by filtration, and dried to give the product (95% yield, 90.3% ee).

Example 33

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N,N*-dimethylamino-1-(4-nitrophenyl)-2-methyl-ethane-1-ol (2.3 g, 10 mmol) and Zn(OTf)₂ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt₃ (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na₂SO₄ and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 60.5% ee).